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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/980,038	11/26/97	KAUFMAN R	211501184US

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EXAMINER	
CELSA, B	
ART UNIT	**PAPER NUMBER**
1654	4

DATE MAILED: 01/21/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/980,038	Applicant(s) Kaufman et al.
	Examiner Bennett Celsa	Group Art Unit 1654

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *17-23, 27, 32, 36, and 102-145* is/are pending in the application.

Of the above, claim(s) *18, 19, 32, 36, 102-106, 108, 109, 114-119, and 12* are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *17, 20-23, 27, 107, 110-113, and 120* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5-7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 17-23, 27, 32, 36 and 102-145 are currently pending.

Claims 18-19, 32, 36, 102-106, 108-109, 114-119 and 121-145 are withdrawn from consideration as being directed to a nonelected invention.

Claims 17, 20-23, 27, 107, 110-113 and 120 are under consideration.

Election/Restriction

1. Applicant's election with traverse of the Group III invention (claims 17, 20-23 and 27) in Paper No. 10 is acknowledged. The traversal is on the ground(s) that Group III and VI should be examined together since they are not independent and distinct. This is not found persuasive for the reasons recited in the restriction requirement e.g. the proteins comprise different lenght and content of amino acids (e.g.. different structure) and different physicochemical characteristics; menas of manufacture (e.g. different recombinant constructs); different use etc. Applicna further argues that claim 32 is further claiming the "thrombin activated protein of claim 17" and thus are neither independent or distinct. However, it is clear that claim 17 requires different substitutions (e.g. Arg 740) and deletions (e.g. Vw binding site) not required by the protein of claim 32 and claim 32 requires a functional limitation which doesn't necessitate the modifications of claim 17. In other words Claims 17 and 32 encompass different protein structure and/or conformations and/or properties as poited out in the restriction. Applicant further argues that there is not a serious burden of searching both the Group III and VI inventions due to similarities in classification. However, as pointed out in the restriction requirement, different literature and/or

sequence searches would result in a burdensome search especially due to the above recited difference in amino acid structure, function, properties and manufacture of the different proteins within groups III and VI. Accordingly, Groups III and VI will not be grouped together. Applicant further argues that that claims 18 and 19 should be examined with Groups III and VI as being dependent on independent claim 17 and further defining the protein of claim 17. However, as again noted, the restriction provides reasons e.g. as to differences among protein structure (e.g. amino acid content and/or length), physicochemical properties, method of manufacture would differ among the proteins of Groups III, VI, XI (claim 18) and XIV (claim 19) as to result in independent and/or distinct proteins for restriction. Applicant further argues that claim 17 is a "linking claim" without explanation.. It is not understood how claim 17 is viewed by applicant as a means of linking proteins which possess different protein structure, properties and means of manufacture. Linking claims, with regard to restriction, usually is applicable with regard to composition not individual compounds. Accordingly, applicant's bare assertion of a linking claim, without further explanation, is not found persuasive. The requirement is still deemed proper and is therefore made FINAL.

2. The election of Group III (claims 17, 20-23 and 27). It is noted that new claims 107, 110-113 and 120 read on the elected invention.

3. Newly submitted claims 122-145 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Inventions III, VI, XI (claim 18) and XIV (claim 19) and claims 122-145 are related as product and process of use.

The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the process for using the product as claimed can be practiced with another materially different product since the any of the proteins of Groups III, VI, XI and Xiv can be used as well as the use of whole blood transfusions or factor Viii concentrates. Additionally, the product as claimed can be used in a materially different process of using that product such as the use in generating antibodies, diagnostic use and in affinity purification of factor viii protein. The election of group III has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 122-145 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. However, it is noted that in accordance with U.S. practice, upon the allowance of a compound claim within an elected compound invention , the Examiner will *consider rejoinder of* method of use claims which are commensurate in scope to the allowed subject matter pursuant to MPEP 821.04 Rejoinder

4. Accordingly:

a. Claims 17-23, 27, 32, 36 and 102-145 are pending.

B. Claims 17, 20-23, 27, 107, 110-113 and 120 are under consideration.

C. Claims 18-19, 32, 36, 102-106, 108-109, 114-119 and 121-145 are withdrawn from consideration as being directed to a nonelected invention.

Sequence Rule Compliance

It is noted that the present application contain nucleotides and peptides within the purview of the Sequence Rules (e.g. see specification page 23). Accordingly, attached is a "Notice to Comply With the Sequence Listing" setting *an extendable one month period for response*.

Drawings

5. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 17, 20-23, 27, 107, 110-113 and 120 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claims 17 and 107, the structure of the human factor FVIII polypeptide which is modified to attain the "procoagulant-active FVIII protein) is indefinite. One needs to know the starting point (e.g. the initial polypeptide structure) in order to determine a final product which would infringe or not infringe the claim. Thus, the metes and bounds of the final protein are not known if the metes and bounds of the starting polypeptide are not described.

B. In claims 17 and 107, the term "the B domain" lacks antecedent basis.

C. In claims 17 and 107, the term "the von Willebrand factor binding site" lacks antecedent basis.

D. In claims 17 and 107, the term "the A2- and A3- domains" lack antecedent basis.

E. In claims 17 and 107, the phrase "a mutation at Arg740" lacks metes and bound as to what the metes and bounds of such mutations are. Do mutations include a deletion of Arg740 ? Only substitutions of Arg740 ? A covalent modification of the Arg amino acid (e.g. sidechain, peptide bond, hydrogen)? The nature of the mutation (e.g. natural or man-made) is unclear.

F. Claim 22, 23, 112 and 113 the phrase "comprises residues 741 to 794 of wild-type factor FVIII... " and "position 794 ... threonine (and leucine) lacks clear antecedent basis since claims 17 and 107 which require deletion of the B-domain which would include these amino acid residues.

G. Use of the term "comprises residues 741-794" in claims 22 and 112 which is dependent upon claims 21 and 111, respectively requiring a 54 residue spacer is confusing as to how "comprising" which is open ended further modifies the sequence 741-794 which is already restricted to 54 amino acids. In other words, what additional structure is encompassed by the use of the term "comprising" in claims 22 and 112?

H. Use of the term "residue(s)" in claims 21-23 and claims 111-113 should specify "amino acid residues" if that is what is intended. If not, the claim is indefinite as to what structure outside of an "amino acid" is encompassed.

8. Claims 22, 23, 112 and 113 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The phrase "comprises residues 741 to 794 of wild-type factor FVIII... " and "position 794 ... threonine (and leucine)" which include B-domain amino acid residues (up to the entire B-domain) fail to limit claims17 and 107 that requires deletion of the B-domain. Claims 22 and 112 which recite the term "*comprises* residues 741-794" fail to further limit claims 21 and 111, respectively that require the spacer be limited to 54 residues; use of the term "comprising" is open ended and would include a spacer which is larger than 54 amino acid residues. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. .

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claims 17, 27, 107 and 120 are rejected under 35 U.S.C. 102(b) as being anticipated by WPIDS English Abstract 88-362113 of EP 295597 (12/88). The EP reference discloses a factor 8 derivative compound and its preparation in pharmaceuticals for treating hemophilia which lacks both the B domain and the vWF binding site (e.g. lacks 741-1689: wherein the B domain is 741-1648 and the vWF binding site is 1649-1689) and which possesses a mutated Arg-740 which acts an amino acid sequence spacer which connects the A1-A2 segment to the C1-C2 segment..

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 17, 20-22, 27, 107, 110-112 and 120 are rejected under 35 U.S.C. 103(a) as being unpatentable over WPIDS Abstract 88-362113 of EP 295597 (12/88) and Kaufman et al., U.S. Pat. No. 5,451,521 (9/95)..

The EP reference discloses a factor 8 derivative compound and pharmaceuticals for treating hemophilia which lacks both the B domain and the vWF binding site (e.g. lacks 741-1689: wherein the B domain is 741-1648 and the vWF binding site is 1649-1689) and which possesses a mutated Arg-740 which acts an amino acid sequence spacer which connects the A1-A2 segment to the C1-C2 segment. The EP reference differs from the presently claimed invention by failing to

recite the Arg-740 mutation (e.g. Arg to Ala) and the use of a spacer which comprises a B-domain peptide. However, the Kaufman reference discloses the making of procogulant factor VIII derivatives of formula A-X-B wherein A is 1-372 and B is 1690-2332 and X is a linking moiety which may comprise 0-1316 amino acids especially those amino acids selected from the sequence Arg-372 to Ser-1690 with a preferred embodiment incorporating Arg 372-Arg740 (e.g. see col. 8-9). Thus, Kaufman provides motivation to the skilled artisan to attach the A1-A2 heavy chain fragment to the light chain C1-C2 fragment utilizing amino acid linkers derived from the B chain of any length; of which is not critical. The Kaufman reference further teaches the replacement of Arg residues at position 740 (e.g. see Abstract) with non-conservative amino acid substitutions, including Ile, in order to obtain proteolytic resistance (e.g. see col. 2, lines 40-67 and Table II in col. 9). Accordingly, the substitution of Arg 740 with other nonconservative amino acids which possess similar side chain properties to Ile (e.g. aliphatic non-charged e.g. nonpolar), such as alanine or valine would have been obvious to one of ordinary skill in the art who wishes to obtain further proteolytic resistant derivatives. Thus, the modification of the EP reference peptide to incorporate a linking peptide which comprises B-chain residues and the further substitution of Arg with aliphatic non-charged amino acid residues (e.g. Ile, Val or Ala) would have been obviious in view of the teaching of the Kaufman reference to use such modifications in order to make procoagulant proteins.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (703)308-0254.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa

January 19, 1999

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/940,038			

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below a communication from the EXAMINER in charge of this application

Commissioner of Patents

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

2. Any inquiry concerning this communication should be directed to Examiner Celsa, Art Unit ~~1811~~ 1654 whose telephone number is (703)305-7556.

3. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

4. Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply.

5. APPLICANT IS GIVEN ONE MONTH FROM THE DATE OF THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Application No. 08/980,038

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached marked-up copy of the "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7. Other: _____

Applicant must provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

Please return a copy of this notice with your response.